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Original Article

Tracheal diverticula in advanced cystic fibrosis: Prevalence, features, and outcomes after lung transplantation

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Abstract

Background: Tracheal diverticula (TD) are rare anomalies that may harbor infected secretions, posing potential risk to patients with lung disease. In an end-stage cystic fibrosis (CF) cohort, we describe the characteristics and associated post-lung transplant (LTx) outcomes of TD.
Methods: Pre-transplant computed tomography (CT)'s were reviewed in CF patients undergoing LTx. TD were characterized radiographically and on autopsy when available. Pre-transplant clinical variables and post-transplant outcomes were compared by TD status.
Results: Of 93 patients, 35 (37.6%) had TD. 58% of TD had fat-stranding, and post-mortem TD examinations revealed histology carrying intense submucosal inflammation, and purulent contents that cultured identical species to sputum. There was no difference in post-LTx survival [HR 1.77 (0.82–3.82), $p = 0.147$], bacterial re-colonization, or rejection in patients with TD compared to those without. Patients with TD were more likely to die from infection, but the result was not statistically significant [HR 2.02 (0.62–6.63), $p = 0.245$].
Conclusions: We found a high prevalence of TD in end-stage CF, where diverticula may represent a large-airway bacterial reservoir. TD were not associated with differences in post-LTx outcomes, but given the infectious concerns further investigation is necessary.

Keywords: Lung transplantation; Cystic fibrosis; Tracheal diverticulum; Lung diseases; Pseudomonas infections; Tomography, x-ray computed

1. Introduction

Cystic fibrosis (CF) is the most common life-shortening autosomal recessive disease in Caucasians. In the lower airway, dysfunction of the cystic fibrosis transmembrane regulator (CFTR) protein leads to chronic airway infection, progressive bronchiectasis, and almost invariably either death or lung transplantation (LTx) [1]. Similarly, in the upper airway CFTR dysfunction consistently results in nasal and paranasal sinus disease, where viscous secretions harbor similar bacteria as the

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane regulator; CI, confidence interval; CLAD, chronic lung allograft dysfunction; CT, computed tomography; FEV_1, forced expiratory volume in one second; GERD, gastroesophageal reflux disease; HR, hazard ratio; LTx, lung transplantation; MD, multiple diverticula; OR, odds ratio; PH, proportional Hazards; SD, standard deviation; Spp, species; TD, tracheal diverticula.

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lungs, posing threat of maintaining infectious colonization, precipitating exacerbations, and impacting outcomes after LTx [2–7].

Although CF-associated sinonasal pathology is well-recognized, little is known about other sites of non-parenchymal airway involvement. Recently, two series have described tracheal diverticula (TD) in CF cohorts with mild-to-moderate lung disease [8–11]. This rare condition, characterized by single or multiple invaginations of the tracheal wall, has a prevalence in the general population of 0.5–2% [12–14]. In patients with lung disease, it has been speculated that TD may arise from chronic cough leading to mucosal herniation through an inflamed tracheal wall [13]. A much higher prevalence was reported in each of the recent series, with TD found in 18% and 28% of CF patients studied [8,9].

The pathogenesis and clinical implications of TD in CF are unknown. TD in the general population have been reported, based on imaging findings, to retain secretions and serve as infectious reservoirs, thus creating risk of secondary mucosal irritation or lower airway microbiologic seeding [14–16]. This may be particularly relevant in CF, where the potential for TD to harbor chronic infection could impact pulmonary disease progression or, importantly, the safety of LTx, after which the infectious risks may be poorly tolerated [9,10].

In this study we aimed to describe for the first time not only the prevalence, but also detailed radiographic and pathologic characteristics, clinical risk factors, microbiology, and post-transplant clinical course associated with TD in a CF cohort with advanced pulmonary disease undergoing LTx.

2. Materials and methods

2.1. Population and data

We performed a retrospective study of CF patients who underwent LTx at our institution between May 1993–December 2015. Our program serves a five-state region in the Northwestern United States. *Re*-transplants, heart-lung transplants, and patients with missing pre-transplant computed tomography (CT) data were excluded. The University's Institutional Review Board approved the study without patient consent.

Clinical data were abstracted from the electronic medical record. Pre-transplant covariates were taken nearest to (always within three months of) LTx date, including: Age, gender, forced expiratory volume in one second (FEV_1), body mass index (BMI), medications, insulin-requiring diabetes status, history of sinus surgery, and gastroesophageal reflux disease (GERD) status (defined by treatment with acid-suppressive medication). CF genotypes were obtained from the local CF Foundation patient portal. Pre-transplant infectious colonization was determined by reviewing the cumulative results of all respiratory cultures in the one year preceding LTx.

Clinical management throughout the study period was guideline-based and directed by our institution's CF and LTx providers as previously described [17], with details regarding routine post-transplant infectious prophylaxis included in the Supplement. Instead of routine post-transplant surveillance bronchoscopy, a clinically-directed protocol was used, where patients underwent bronchoscopy only as clinically indicated, as previously described [18].

Because a clinically-directed post-transplant sampling protocol was used, throughout the study period cultures were obtained only when patients exhibited new symptoms, radiographic abnormalities, decline in spirometry, or other clinical changes as determined by treating providers. For this study, post-transplant infectious re-colonization was evaluated at three and twelve months after LTx by reviewing all post-transplant respiratory cultures in the preceding interval (sputum/aspirates, bronchial washings, bronchoalveolar lavage). As previously described, graft re-colonization at those time points was defined as repeated detection, on at least two occasions, of organisms grown pre-transplant regardless of the presence of infectious signs [19].

Causes of death were obtained from the United Network for Organ Sharing and verified by chart review. Post-transplant airway complications were defined as any requirement for bronchoscopic intervention including debridement, dilation, or stenting. Acute rejection episodes and chronic lung allograft dysfunction (CLAD) status were assessed in all patients by review of records by a transplant pulmonologist who was blinded at the time to TD data: Acute rejection was defined histologically on transbronchial biopsy (any positive A, B grades), and separately by treated episodes (including those lacking histologic confirmation). CLAD was defined as a sustained, $\geq 20\%$ decline in FEV_1 as compared with the average of the two best post-transplant FEV_1 values, in the absence of clinical confounders [20].

2.2. Imaging protocol

Patients underwent non-contrast chest CT prior to LTx listing, repeated annually and as clinically indicated until LTx. Following LTx, CTs were performed as clinically indicated. Images were acquired on 64-MDCT scanners (LightSpeed-VCT, GE-Medical). Axial images were reconstructed at 1.25–5.0 mm thickness. Image processing used PACS (Centricity, GE-Medical). The pre-transplant CT (for primary analyses) was defined as the one nearest to LTx. Images were reviewed by an attending thoracic radiologist blinded to clinical data. Based on previously described criteria [8,13], the presence of TD were established when a round, oval, or tubular mediastinal structure was seen outside the esophagus and abutting the tracheal wall, containing air and/or fluid (with CT attenuation different from the mediastinum). Patients with any number of TD on pre-transplant CT were labeled as having TD, and those with ≥ 2 as "multiple diverticula" (MD). The unexposed group was defined as patients without TD. Diverticular characteristics were reviewed including: Size, density, presence of fat-stranding, and percentage air-filled (for air-containing diverticula). Location was labeled typical if at the right thoracic inlet, and atypical if located elsewhere [13].

In a subcohort of patients with post-transplant CT's available, the most recent scans were reviewed to calculate post-transplant TD prevalence. For patients missing pre-transplant scans (excluded

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